



No price too high?

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NO PRICE TOO HIGH?

ALGLUCERASE offers the first real hope of reversing the glycolipid deposition responsible for the painful and sometimes life-threatening complications of Gaucher's disease. Because it is both uniquely promising and remarkably expensive, it poses stark dilemmas for patients, legislators, and physicians. Many patients treated with alglucerase risk the loss of their private health insurance coverage because they are likely to exceed its limits. Congress, which passed the Orphan Drug Act to encourage the development of treatments for uncommon conditions like Gaucher's disease, is now debating whether the act goes too far to protect the profits of pharmaceutical companies. Policy makers and physicians who believe that cost should not be a consideration in deciding whether to approve or administer a promising treatment face a severe test of their conviction.

The standard regimen of alglucerase, devised by researchers at the National Institutes of Health (NIH),¹ can cost hundreds of thousands of dollars annually per patient during the first phase of treatment. This phase, which usually lasts from 6 to 24 months, is followed by a lifelong maintenance phase at a lower dosage. NIH researchers hope to reduce the maintenance dosage to as little as 7.5 U per kilogram of body weight every two weeks² — well below the dosages reported in the literature. At this low dose, the treatment still costs tens of thousands of dollars each year. Even bone marrow transplantation, once regarded as the most aggressive treatment for seriously ill patients with Gaucher's disease, costs less.

Few patients pay these costs directly. Most have private health insurance policies that cover all but a fraction of the costs.³ But these policies usually specify a lifetime ceiling on health benefits (most commonly \$1 million), and those who receive high-dose alglucerase regimens can reach the ceiling in two or three years. Thus, the costs of alglucerase therapy will frequently exhaust insurance benefits, and because nearly all private insurance plans either exclude coverage

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for preexisting conditions or refuse to enroll persons who have a serious disease, patients who lose their insurance usually remain uninsured.

Alglucerase could be administered at lower cost if the price were lower or if less of it were used in treatment. In a study reported in this issue of the *Journal*, Figueroa and his colleagues at the Scripps Clinic tested the latter approach.⁴ In an ingenious application of their hypothesis⁵ that high-affinity receptors for glucocerebrosidase are rapidly saturated at the doses used in previous studies, the Scripps group tested a high-frequency ("fractionated") alglucerase-sparing regimen.⁴ Their regimen appears to be as effective as the NIH regimen. Because the dosing schedule for the Scripps regimen is much less convenient than the leading alternatives and adds at least \$6,500 to the annual costs of intravenous infusion, in other circumstances it would be a mere curiosity. But for a 70-kg adult, it can save \$300,000 in drug costs in the first year.

The published studies do not definitively establish the therapeutic equivalence of the NIH and Scripps regimens. The NIH patients may have had larger loads of accumulated glycolipid than the Scripps patients. Subtle differences in the effectiveness of alternative modes of administering alglucerase could have escaped detection. Larger and longer-term studies that carefully control for patients' characteristics will be needed to learn more about the effectiveness of each regimen. But without compelling evidence that an alternative regimen is superior, perhaps the regimen that costs hundreds of thousands of dollars less should be considered the new standard.

Even with the Scripps regimen, outlays for a 70-kg patient exceed \$70,000 annually, about as much as for the lowest-dosage maintenance regimens proposed by the NIH researchers. Why is the price so high? The costs of research and development for new drugs, though difficult to measure, are usually substantial. According to industry spokespersons, pharmaceutical companies spend an average of \$231 million (in 1987 dollars) to bring a "new clinical entity" to market.⁶ In the treatment of a rare condition, these costs must be recovered from few patients, making a low price infeasible. The pharmaceutical manufacturer must also recover production costs. Manufacturing usually accounts for a small share of the cost of producing a drug, but alglucerase may be an exception. Currently, alglucerase is derived from placental extracts, and Genzyme, the manufacturer, claims that its production costs are extremely high.

The price can be high, however, even if the costs of research, development, and manufacturing are not. Every American pharmaceutical company has an obligation to its shareholders to maximize profits, just as it has a mission to make safe and effective treatments available to patients. By greatly weakening the forces that ordinarily restrain the sellers of goods and products from charging high prices, our health care system sometimes awards manufacturers higher profits when they charge higher prices. If an automobile manufac-

turer charges too much, consumers will buy cars from its competitors, and profits will fall. The manufacturer of alglucerase did not face competition of this kind, because the provisions of the Orphan Drug Act gave it a seven-year monopoly on the sale of alglucerase for the approved indications. A monopoly alone need not lead to very high prices; in many other industries, consumers refuse to buy the product when monopolists charge too much. Undoubtedly, if patients with Gaucher's disease had to pay for alglucerase out of pocket, few could or would. But in this case insurers, not patients, pay most of the charges.

Insurers have strong reasons for refusing to pay too high a price. Most pay because they must; their contracts obligate them to cover their share of the charges for any drug approved by the Food and Drug Administration. When a single seller faces many buyers who will pay whatever price the seller asks, high prices are inevitable, whether production costs are high or low.

High prices do not ensure profitability. Manufacturing costs and the investment in research and development can exceed revenues even when the price is high. However, the substantial federal role in the development of alglucerase greatly increased the chance that the manufacturer would recover its costs. NIH investigators invented the compound and helped to develop its manufacturing process. The NIH also sponsored or performed much of the research that led to the drug's approval. According to the Office of Technology Assessment,³ Genzyme spent less than \$30 million on research and development for alglucerase, or about one eighth the amount typically spent to develop a new drug.

A preoccupation with profits sometimes diverts the attention of legislators and other government officials from a more basic consideration. If such officials conclude that a high price is warranted as long as the profits are not "excessive," they encourage the development of costly, high-profile treatments and blunt the incentives for drug companies to develop efficient methods of production. Manufacturers may be tempted to release new drugs before the production process has been perfected. Discouraging high profits while tolerating high prices serves neither the interests of patients nor those of the companies that develop and produce new forms of medical technology. The fundamental question is not whether the treatment is profitable, but whether it is worth what it costs.

The health care systems of every nation confront this question. All countries withhold some treatments from some people who might benefit from them. The differences lie in the way decisions about the value of specific health care techniques are made and implemented. Some countries explicitly restrict access to expensive forms of technology, and some regulate prices directly. Others set global budgets for health care and allow regional authorities, hospitals, or other providers to make decisions about their implementation. In the United States, with its multitude of payers

and providers, decisions about the value of health care techniques are often implicit and fragmented. The United States has no coordinated strategy for controlling the availability of safe and effective techniques, regulating their prices, or capping health care expenditures. Consequently, medical innovations flourish in the marketplace, enabling American manufacturers to lead in the development of new drugs and devices, and Americans spend far more on medical care than the citizens of any other country. Dramatic advances in molecular biology promise to make both these features of American health care more prominent. Because major technological advances coincide with unprecedented public distress at rising health expenditures, policy makers, payers, and physicians face increasingly difficult choices.

Providing access to new and established forms of technology and health care while controlling expenditures is the paramount challenge facing American medicine. Sometimes scientific advances, like those of the Scripps group, make the task easier by lowering the cost of effective care. But we cannot expect advances in biomedical science to spare us from hard decisions. The need to make choices will compel us to weigh the costs and benefits of technological innova-

tions and sometimes to conclude that a promising or effective treatment is just too expensive. Drawing such conclusions can be difficult, and acting on them painful. But if patients and payers never say no, we cannot blame the producers of medical advances for inferring that no price is too high.

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REFERENCES

1. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency — macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med* 1991;324:1464-70.
2. Barton NW, Brady RO, Murray GJ, et al. Enzyme-replacement therapy for Gaucher's disease. *N Engl J Med* 1991;325:1811.
3. Garber AM, Clarke AE, Goldman DP, Gluck ME. Federal and private roles in the development and provision of alglucerase therapy for Gaucher disease. Office of Technology Assessment, U.S. Congress. Washington, D.C.: Government Printing Office, 1992.
4. Figueroa ML, Rosenbloom BE, Kay AC, et al. A less costly regimen of alglucerase to treat Gaucher's disease. *N Engl J Med* 1992;327:1632-6.
5. Beutler E, Kay A, Saven A, et al. Enzyme replacement therapy for Gaucher disease. *Blood* 1991;78:1183-9.
6. Annual report, 1992. Washington, D.C.: Pharmaceutical Manufacturers Association, 1992.

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BARBITURATES IN THE CARE OF THE TERMINALLY ILL

BARBITURATES are well known for their capacity to cause death reliably and painlessly and for their efficacy in producing unconsciousness before the administration of other lethal drugs. Barbiturates are used in the execution of prisoners by lethal injection,¹ are commonly employed by Dutch physicians in performing euthanasia,² and have played a part in reported cases of assisted suicide in the United States.^{3,4} A recent best-selling book recommends barbiturates as a reliable method of suicide for the terminally ill.⁵

Physicians also administer barbiturates to the terminally ill without intending that they be used to cause the death of the patient. Even in these circumstances, however, the unavoidable side effects of the drugs may hasten the patient's death, and care givers may be uncertain about whether their actions will be viewed as killing or caring. In this article, we review situations in which the nonlethal use of barbiturates may be indicated and discuss situations in which their administration can be morally justified. We also provide practical advice for the use of these agents.

CASE REPORTS

Patient 1 was a 28-year-old woman with a retroperitoneal soft-tissue sarcoma that arose as a second cancer after she had been successfully treated for a rhab-

domyosarcoma of the cervix and vagina at the age of 14. Despite surgical excision and chemotherapy, her second tumor spread locally, metastasized to her spine and lungs, and eventually invaded her spinal canal from T11 to L3. The intensity of her pain increased steadily. Maximal-dose radiation therapy had already been administered, and decompressive surgery was not feasible because of the size of the tumor. Trials of phenytoin and lorazepam were without benefit. A fentanyl infusion produced only partial relief.

A subarachnoid catheter was placed below the site of the tumor, and an infusion of bupivacaine diminished her leg spasms, but did not result in sensory analgesia in dermatomes above T11 because of a near-complete spinal block at approximately L1. A subarachnoid injection of phenol at T7-T8 also failed to provide adequate pain relief.

Her pain became so severe that she relinquished most decision making to her mother, with the understanding that she desired pain control even if it could only be achieved at the cost of sedation. She was then kept in a state of light sedation (with intermittent arousability to voice) with a fentanyl infusion (at a rate roughly corresponding to 5000 mg of morphine per hour⁶), nitrous oxide (50 percent in oxygen) by face mask,⁷ and a methohexital infusion (loading dose, 2 mg per kilogram of body weight; infusion, 4 to 5 mg per kilogram per hour) until she died of progressive hypoxemia two days later.

Patient 2 was a 19-year-old woman who for nine years had had an astrocytoma that now involved her brain stem and cervical spinal cord. As her tumor